

NewbornScreeningNews

A NEWSLETTER OF THE NEWBORN SCREENING PROGRAM AND THE NEWBORN SCREENING LABORATORY

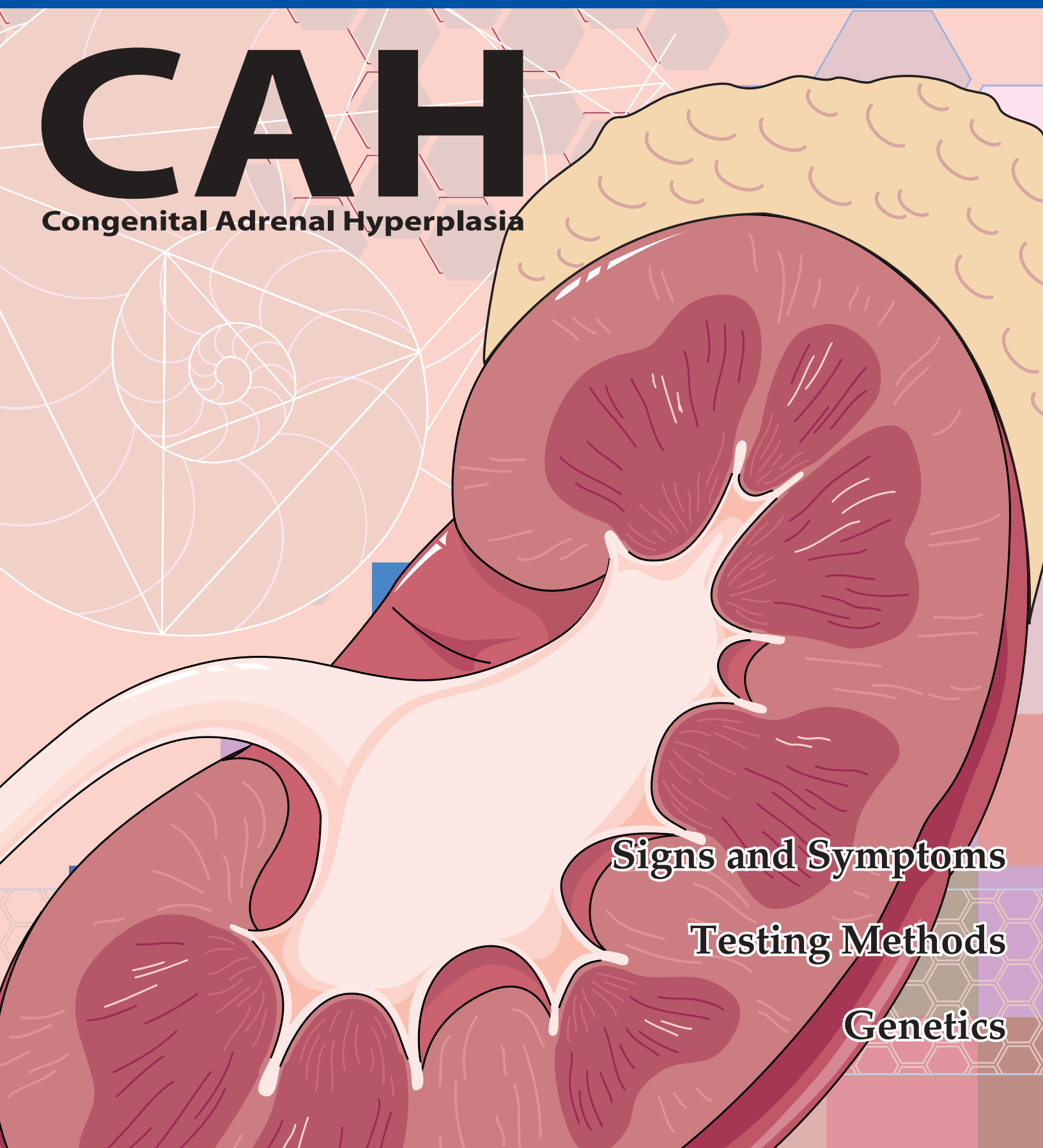
CAH

Congenital Adrenal Hyperplasia

Signs and Symptoms

Testing Methods

Genetics



CONGENITAL ADRENAL HYPERPLASIA (21-HYDROXYLASE DEFICIENCY)

❖ By Mike T. Swinyard, MD

Infant death from salt loss in both boys and girls...Male gender assignment for baby girls. Such can be the consequences of a missed or delayed diagnosis of 21-hydroxylase deficiency, the most common cause of congenital adrenal hyperplasia (CAH).

CAH is a group of several inherited diseases, each caused by a specific defect in one of the many enzymes required for the biosynthesis of cortisol and aldosterone. 21-hydroxylase is one of these enzymes. Based on the population studied, 21-hydroxylase deficiency may constitute 90% or more of all cases of CAH. Therefore, in this article CAH will be used synonymously with 21-hydroxylase deficiency.

CLINICAL PRESENTATIONS. It is helpful to describe the relative severity of CAH, qualitatively, according to the symptoms and signs at the time of initial presentation. Two distinct clinical forms in infants have been described: the **simple virilizing form** (no salt loss) and the more severe, **salt-losing form**. This classification approach has its clinical utility, but it should be kept in mind that CAH, both phenotypically and genotypically, is a more complex disease. This complexity is manifested in the significant overlap between these two forms and in the attempts to define them based on available parameters. Genetic analysis may help clarify these and other forms of CAH.

In both forms of CAH, the adrenals are unable to produce sufficient cortisol (hydrocortisone). Decreased cortisol production leads to a compensatory increase in ACTH secretion and hyperplasia of the adrenal cortex. This futile ACTH drive escalates the build up of steroid precursors proximal to the 21-hydroxylase enzyme block. These

excess metabolites are converted outside the adrenal to active androgens (testosterone and dihydrotestosterone) and, to a much lesser extent, estrogens. The predominance of androgens (in utero) leads to varying degrees of masculinization of affected girls. This is manifested by aberrant posterior fusion of the labia majora and hypertrophy of the clitoris. These findings usually prompt clinicians to investigate further, leading to a specific diagnosis and treatment.

Most affected boys show no overt signs of androgen excess at birth, but experience genital enlargement and rapid growth later in childhood. These signs trigger evaluation, but at a time when adverse consequences of untreated CAH have already occurred.

In the most severe form of CAH, normal aldosterone production is lacking. This leads to progressive

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hyperkalemia, sodium loss, and metabolic acidosis. Dehydration develops, as a consequence of poor feeding, vomiting and diarrhea. Acute adrenal crisis usually occurs between 4 and 15 days of age, resulting in cardiovascular collapse, ventricular dysrhythmias, and cardiac arrest.

Severely affected boys rarely exhibit physical clues of their disease at birth. However, girls with CAH have remarkable clitoral enlargement and labial fusion and may be incorrectly labeled as boys.

Until an astute examiner questions the infant's male gender (after failing to locate testicles in their expected location), the female is erroneously assigned a male gender. Another clue

to their proper gender is the presence of a uterus on pelvic ultrasound.

DIAGNOSIS. When a positive screening test is received, prompt evaluation is a must. This includes a feeding history, body weight, vital signs, and complete physical exam with emphasis on assessment of hydration. Particular attention is also paid to the genital exam for possible sexual ambiguity (clitoromegaly and labial fusion in a presumed girl; micro-phallus and cryptorchidism in a presumed boy). In term girls, clitoromegaly would be suspected, if the clitoris is visible with the legs adducted. Inconsistencies of the genital exam with the presumed gender of the baby should alert the clinician to the possibility of incorrect gender assignment (e.g. absent testicles in a presumed boy).

Laboratory evaluation should include a serum 17-hydroxyprogesterone level. A basic metabolic panel should be considered.


Diagnosis is based on an elevated 17-hydroxyprogesterone level, considering the reference range of the lab for estimated gestational and postnatal age.

TREATMENT AND OUTCOMES. Treatment consists of lifelong hormone replacement with hydrocortisone. Patients who have the salt-losing form also require fludrocortisone. Most salt-losing infants need sodium chloride supplementation, due to the salt deficiency which develops when they present and due to ongoing sodium needs not met by low-sodium sources of infant nutrition (human milk and commercial infant formulas). Additionally, virilized girls may need surgical reconstruction of the external and/or internal genitalia.

Affected families should receive genetic counseling and guidance regarding recurrence risk, molecular analysis of the 21-hydroxylase gene

with identification of the specific mutation(s) in their kindred and, if desired, prenatal diagnosis and treatment to minimize virilization of affected female fetuses in future pregnancies.

Goals of treatment include maintenance of a normal growth pattern, appropriate onset and progression of puberty and prevention of adrenal crisis with acute childhood illnesses. In patients who have reached their final height, avoidance of iatrogenic Cushing's syndrome is also important.

These goals are generally, but not always met. Poor outcomes have been attributed to undertreatment, secondary to poor adherence to prescribed dosage regimens, and overtreatment, from excessive maintenance doses of glucocorticoids, and the use of potent, long-acting medications (prednisone or dexamethasone). 

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♦ Mike T. Swinyard, MD, Board Certified Pediatric Endocrinologist

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www.health.utah.gov/newbornscreening

CAH Follow-up

• By Angie Livingston, RN

The purpose of universal newborn screening is to identify at-risk infants in a timely manner and assure that these infants receive appropriate follow-up care. The high risk for morbidity and mortality associated with Congenital Adrenal Hyperplasia (CAH) and the availability of a screening test and evidence-based treatment models fits the guidelines for addition to the Utah newborn screening battery of tests.

Utah uses a two-tier laboratory testing system to identify at-risk infants. If an infant fails both tiers of the screening system, follow-up activities begin with the immediate referral by the Newborn Screening follow-up nurse. The nurse evaluates the lab result based on the infant's birth weight. Because low birth weights and stress are associated with increased levels of 17-OHP different follow up protocols are used based on infants clinical status at time of blood collection. If the infant weighted less than 1500 gram or is receiving treatment in a neonatal intensive care a second specimen is requested. This recall second specimen depicts a trend of 17-OHP levels. If the recall second specimen is normal, the result is not consistent with CAH. If the recall second specimen is still abnormal, the confirmatory testing process beings.

Confirmatory testing consists of a serum 17-OHP level which is done by ESOTERIX laboratory in California. The blood specimen must be separated

and frozen prior to transport. The Newborn Screening follow-up nurse arranges for the collection and transport of the serum for 17-OHP level testing.

Follow-up of CAH is complex and requires coordination between the newborn screening program, the pediatric endocrinology consultants, the medical home, and laboratory personnel who collect and submit screening and diagnostic specimens. To insure appropriate and timely identification and follow-up of an at-risk infant please note the following:

The birth weight of the infant is essential in interpreting screening results. Please make sure to include the birth weight, in grams, of the infant when submitting the newborn screening specimen.

Timely submission of specimens is required for effective screening. The first specimen should be collected when the infant is 48 hours old, or within 4 hours of discharge from hospital. Delays in collecting the specimen or submitting specimen can negatively impact the infant's health. Each hospital should consider sending specimens by courier to decrease delay time between specimen collection and specimen testing.

Complete and accurate demographic information assists the follow-up nurse in locating the infant and the infant's medical home. Fill out screening cards completely and accurately.

Diagnostic testing is arranged through the newborn screening program. The laboratory collecting the specimen and the medical home will be notified with instructions on proper specimen collection and processing. The newborn screening program pays for specimen collection, specimen processing and transport, and diagnostic testing. Please read and follow instructions carefully.

Newborn screening for CAH is a team effort. The newborn screening follow-up program appreciates your dedication to providing quality care to Utah's newborn population.

♦ Angie Livingston, RN is one of Utah Newborn Screening Program's nurses.

Do you need additional copies?

Call the Newborn Screening Program to obtain additional copies for your staff or colleagues at

801-584-8256 or at

www.health.utah.gov/newbornscreening



What causes congenital adrenal hyperplasia (CAH)?

CAH represents a group of autosomal recessive conditions. Classic CAH is caused by mutations in the CYP21 gene located on chromosome 6. CYP21 encodes the enzyme, 21-hydroxylase. Mutations (changes) in this gene cause the gene to not function properly, thus leading to a deficient enzyme product. This enzyme is needed by the adrenal gland to make the major steroid hormones of the adrenal cortex: cortisol and aldosterone. Without these hormones, steroids are 'diverted' to becoming androgens, a form of male sex hormones. This causes early (or inappropriate) appearance of male characteristics. In newborn females, this manifests as enlarged clitoris (virilization).

Typically, individuals have two normal copies of the CYP21 gene. Individuals with CAH have mutations in both copies of the gene. Individuals who have one normal gene and one abnormal gene with a mutation are called 'carriers'. Carriers have approximately 50% of enzyme activity level, yet do not have symptoms of CAH and do not require treatment.

What are the chances of having another child with CAH?

Both parents of a child with CAH are carriers of CAH (one normal gene/one abnormal gene). As both parents are carriers of a condition, there is a 25% chance (1 in 4) of having another child (boy or girl) with CAH with each pregnancy (see picture). Individuals who have had a previous child with classic CAH and are planning on having more children should discuss prenatal treatment options with their obstetrician.

What are the risks for other family members?

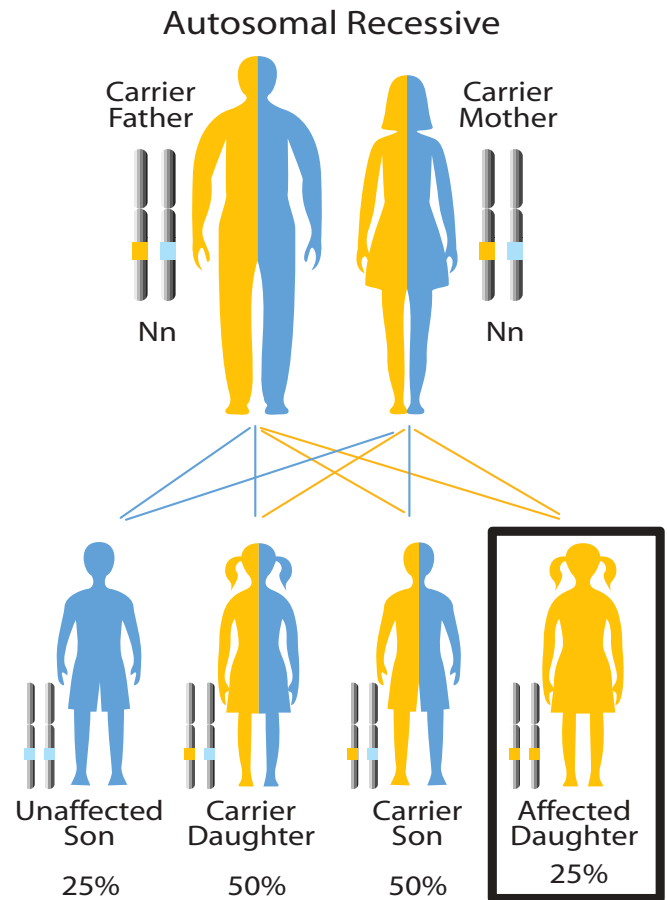
The chance of other family members having a child with CAH depends on the carrier status of both parents. The chance that someone in the general population is a carrier of classic CAH is approximately 1 in 50 (2% of the population). (Of note, the chance that someone is a carrier of non-classical CAH is approximately 1 in 15). Given this information, the individual with CAH has a 1 in 100 (1%) chance of having a child with this condition. Siblings of the affected child have a 2/3 chance of being a carrier. Aunts and uncles of the affected child (siblings of the parents) have a 50% chance of being a carrier. Carriers can sometimes be identified through the ACTH stimulation test, although DNA testing is more accurate and is usually the recommended test if the mutations within the family are known. The sensitivity for detecting mutations within the CYP21 gene is 80-95%. If other family members or their partners are interested in learning their carrier status, they can contact the Metabolic Genetics clinic at 801-585-2457.

Where can I find more information?

Congenital Adrenal Hyperplasia Education and Support Network
www.congenitaladrenalhyperplasia.org

CARES Foundation - Congenital Adrenal hyperplasia Research Education and Support
www.caresfoundation.org

♦ Pilar Lenglet, MS, CGC, University of Utah, Division of Medical Genetics.



Key Points of CAH

- Two forms of CAH: The simple virilizing form (no salt loss) and the more severe, salt-losing form.
- In CAH, the adrenals are unable to produce sufficient cortisol.
- Decreased cortisol production leads to a compensatory increase in ACTH secretion and hyperplasia of the adrenal cortex.
- Excess metabolites are converted outside the adrenal to active androgens (testosterone and dihydrotestosterone) and to a much lesser extent, estrogens.
- The predominance of androgens leads to varying degrees of masculinization of affected girls in utero.
- In severe CAH, normal aldosterone production is lacking.
- Clinical findings: hyperkalemia, sodium loss and metabolic acidosis.
- Acute adrenal crisis usually occurs between 4 and 15 days of age resulting in cardiovascular collapse, ventricular dysrhythmias and cardiac arrest.

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www.istockphoto.com

Check out the following websites for more information on CAH and newborn screening.



Utah Department of Health, Newborn Screening Follow Up Program

<http://health.utah.gov/newbornscreening>



Congenital Adrenal Hyperplasia Education and Support Network

www.congenitaladrenalpherplasia.org

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CAH

Congenital Adrenal Hyperplasia

Quick Facts

- Congenital Adrenal Hyperplasia is a deficiency of the enzyme 21-hydroxylase.
- Infants may be clinically identified before newborn screening testing is completed:
Ambiguous genitalia, salt wasting crisis, hyperkalemia, metabolic acidosis.
- Lifelong treatment may consist of prescribed doses of cortisol, electrolytes, ACTH and reconstructive surgery for females with ambiguous genitalia.
- Parents who have a child with Congenital Adrenal Hyperplasia have a 1 in 4 or 25% chance with each pregnancy of having another child with CAH deficiency.
- Two forms of CAH exist:

Salt-Wasting

- Adrenals are not able to produce sufficient cortisol.
- Virilization of the genitalia in females sometimes presenting with clitoromegaly and labial fusion. In boys, microphallus and cryptorchidism.
- Adrenal crisis.
- Precocious growth.
- Hyperkalemia, sodium loss, metabolic acidosis dehydration, vomiting and diarrhea, cardiovascular collapse, ventricular dysrhythmias cardiac arrest

Simple Virilization

- Adrenals are not able to produce sufficient cortisol.
- Sometimes asymptomatic.
- Premature pubic hair growth.
- Childhood acne or hirsutism.

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